Refer to: Arsenic poisoning—Medical Staff Conference, University of California, San Francisco. Calif Med 118:13-17, Mar 1973

Arsenic Poisoning

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* *The topic for presentation this morning at Medical Grand Rounds will concern itself with arsenic poisoning. The case summary of the patient will be given by Miss Kathy O'Farrell who is a clinical clerk visiting us from the University of West Virginia School of Medicine.*

MISS KATHY O'FARRELL:† This is the second admission for a 38-year-old white man who presented with complaint of numbness and tingling in his hands and feet that had become progressively more severe during the week preceding admission. The patient had been in good health until, about three weeks before admission, he had sudden onset of headaches, abdominal pain, and diarrhea after cleaning an electroplating tank with lye and refilling it with hydrochloric acid and wetting solution. The same evening he began passing dark urine and light-colored stools. Two days later he began to vomit, and anorexia and a low-grade fever developed. These symptoms led to his first admission here. During that admission, the gastrointestinal symptoms improved, but a right lower lobe infiltrate and skin rash developed, as well as tingling in the fingers and toes. Laboratory studies at that time revealed increased values for serum glutamic oxaloacetic transaminase (SGOT), lactic acid dehydrogenase (LDH), blood urea nitrogen (BUN), and creatinine. Urinalysis revealed 1 plus proteinuria and a positive urinary porphyrin screen. Upper gastrointestinal and gallbladder radiographic series were negative, but endoscopy revealed two superficial posterior wall duodenal ulcers. The patient was discharged after one week in hospital. Over the ensuing days, the numbness and tingling in toes and fingers progressed to involve the legs and forearms, and the patient noted difficulty walking. He was readmitted, and when, a day later, the results of the urine heavy metal screen from the first admission became available, they showed a toxic level of arsenic.

On physical examination the patient appeared alert and anxious and was quite unsteady on his feet. Vital signs were normal, as were results of

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examination of the head, eyes, ears, neck, chest and heart. The abdomen was tender in all areas and the tip of the spleen was palpable. There was no hyperpigmentation of the skin, hyperkeratotic lesions of the palms, or transverse lines under the fingernails. A resolving rash was present on the chest and upper back. Neurological examination revealed moderate distal weakness of all four limbs, loss of vibratory sensation in both the upper and lower extremities, and loss of pain and touch sensation in the feet. The tendon reflexes were 3 plus in the arms and essentially absent in the legs. The gait was severely ataxic.

Admission laboratory data revealed a hemoglobin of 11.7 grams per 100 ml, hematocrit of 35.1, and normal indices. Platelets numbered 407,000 and white blood cells 2700 per cu mm with 61 percent lymphocytes, 21 percent neutrophils and 9 percent eosinophils. Serum electrolytes were normal, the BUN was 22 mg and the creatinine 1.2 mg per 100 ml. The SGOT was 93 units and the LDH 145. The values for BUN, creatinine, and serum enzymes were less than those during the previous admission. Urinalysis, however, still revealed 1 plus proteinuria and a positive porphyrin screen. The cerebrospinal fluid had a glucose content of 79 and a protein content of 77 mg per 100 ml, and there were 6 lymphocytes per high power field. Analysis of pubic hair for arsenic revealed 3.1 parts per million (normal, 0.3 to 0.5) and the urine contained 0.55 parts per million (normal up to 0.02 parts). Electromyograms were consistent with a polyneuropathy of the dying back type. During the patient's stay in hospital, the leukocyte count dropped to 1,900 per cu mm at one point, with 8 percent neutrophils and 20 percent eosinophils. At the time of discharge, the count was 3,000 per cu mm. Platelets remained within the normal range. Results of liver function tests returned to normal, the right lower lobe infiltrate cleared, and the patient's appetite improved, but he began having frequent leg cramps. British antilewisite (BAL) therapy was not instituted, because of the three-week time lapse since his exposure. Since his discharge [two weeks previously at the time of this presentation] the neurological status has remained essentially unchanged but severe persistent leg cramps have developed that are unresponsive to quinine and prevent his being here today. Analysis of the old and fresh hydrochloric acid solutions and the wetting solutions to which he was exposed revealed trace amounts of arsenic, antimony and phosphate.

DR. SMITH: *Thank you, Miss O'Farrell. This patient was presented to me as an unknown on medical ward rounds. I am told that he represents a classic case of arsenic poisoning. I can assure you that I noted the ill-concealed delight on the faces of the house staff as I went down to crashing defeat trying to tie together porphyria, multiple system disease, leukopenia, and neuropathy, all of which are so typical of this syndrome to those who know it. Fortunately, we have someone here today who is well informed with respect to this syndrome. He is Dr. Arthur Asbury, Vice-chairman of the Department of Neurology and Chief of Neurology at Fort Miley Veterans Administration Hospital, who will tell us how we should go about recognizing this syndrome in the future.*

DR. ASBURY:* Thank you, Dr. Smith. I only hope that I am able to recognize it in the future. I trust that some of the remarks I make this morning will help you do the same. I have seen the patient, who unfortunately cannot be here today. He still has leg cramps, and it was felt inadvisable to ask him to make the trek although he does live in the Bay Area. I shall try to bring him into my discussion at each point along the way so as to pull the case together particularly for those who have seen him on the ward and know him best.

Perspective

I shall start out by giving you some historical perspective of arsenic intoxication. Arsenic is synonymous in the public mind with poison, and actually today the majority of cases of arsenic intoxication are from attempts at homicide or suicide, though some are accidental. Some of them are iatrogenic, especially in less well-developed areas, where arsenic-containing compounds are still used medicinally. For example, Fowler's solution which contains potassium arsenite in rather generous quantities is sometimes used for psoriasis. Arsenic was well known to the ancients in Galenic times and was prescribed mainly in the form of the yellow compound orpiment (arsenous sulfide). It occurs naturally and has been mined for many years as a pyrite mixure. In the Renaissance era, orpiment was used as a poison and particularly by the Borgias, who said they favored it. In my reading about the forensic aspects of arsenic intoxication, I came across an interesting paragraph in a book by a man named John Glaister

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who was a forensic pathologist in Scotland (Glaister, J., "The Power of Poison," Cristopher Johnson Publishers, London, 1954, p. 79). He writes as follows:

> About 1659 a wave of suspicious poisoning broke out in Rome when many married men died, and the incidence of young widowhood mounted. The deaths of many of the husbands were closely linked with the fact that they had been peculiarly unaccommodating so far as their wives were concerned. The government on taking a stand and investigating the whole affair, disclosed a nest of young wives directed by an old woman named Spara. This Sicilian, so far as the art of poisoning was concerned, was an apt pupil of an infamous woman called Toffania who sold the poison, although she gave her preparations away without payment to such wives as wished to have other husbands. It is said that Toffania distributed her poison in small glass phials ornamented with the image of a saint. The aqua Toffania was said to be crystallized arsenic. The whole of this coterie of young women was arrested and put to torture. Old Spara and four others were publicly hanged. Toffania lived to a very old age, but finally having been taken from a monastery where she had hidden, was put to torture, confessed her crimes, and was strangled.

So there is an insight into another time, the 17th century. Perhaps when we become concerned with violence in our own age, it is well to reflect back on others.

Systemic Effects of Arsenic Intoxication

Let us now consider the systemic effects of arsenic intoxication. An acute toxic dose of arsenic is approximately 100 mg as arsenous oxide. Patients receiving much more than this are likely to die in the first 12 hours with overwhelming gastroenteritis, cardiac collapse, myocardial failure, and coma, often with convulsions as well. Patients who have had massive doses are probably not salvagable, but fortunately such instances are rarely seen. More common among patients seen in the emergency room is the sub-lethal dose, and usually the clinical story goes something like this. A few hours after an acute single ingestion or exposure to dust, acute and often violent gastroenteritis develops, with severe generalized body and stomach cramps and pernicious vomiting, then rice-water diarrhea. In days gone by, the patients died in the throes of gastroenteritis, but today, with fluid replacement, patients can usually be brought through this stage even though the diagnosis may not be known. Interestingly, arsenous oxide is as radiopaque as barium, and an alert clinician sometimes can make the diagnosis of arsenic ingestion from a plain film of the abdomen taken during the work-up of the gastroenteritis. There is a nice little note in the New England Journal of Medicine in 1962 by Hilfer and Mandel,[1] documenting just such an instance. Over the next day or two, the patients may become icteric and have a greater or lesser degree of hepatic necrosis. In addition, they usually have severe irritation of mucous membranes with a feeling of very tight constriction in the throat, profuse hyperhidrosis, tearing, and increased salivation. In fact, some patients have complained of scalding tears—tears that irritate the skin as they roll down the cheek—as a feature of the increased glandular activity of the mucous membranes. The skin often manifests the effects of arsenic intoxication, and the variety of rashes that have been described are legion. Generally, in acute intoxication, the rash is erythematous and in no way diagnostic of the condition. However, in chronic arsenic intoxication, hyperpigmentation is the rule and often it is attended by keratosis, particularly of the palms and soles, with characteristic cracking and fissuring of the skin. There are many illustrations published in the literature of huge pieces of skin peeling away from the palms in such patients.

Chronic Arsenic Intoxication

The features of chronic arsenic intoxication are beautifully described by Kelynack and his colleagues in an article in the Lancet in 1900.[2] Kelynack, the senior medical registrar at Manchester, awoke to the possibility that the presumed alcoholic peripheral neuritis in a large number of patients they were seeing in Manchester and adjacent towns might in fact be due to arsenic intoxication. In a period of six or eight months they saw several thousand patients, of whom about 70 died. On looking into the matter from the epidemiological standpoint, they found that most of the patients were from the poor working classes and that they drank large quantities of beer. On analysis, the beer was found to contain large quantities of arsenic. The brewers were approached, and when the various ingredients of the beer were analyzed, it turned out that all the invert sugars and dextrose that went into the beer were generously laced with arsenic, apparently derived from the sulfuric acid used to pro-

duce the sugars. In those times the pyrites used in making sulfuric acid contained over 2 percent arsenic. The cutaneous manifestations and the characteristics of the neuropathy are memorably described in the Kelynack paper. In addition to the hepatic necrosis, renal tubular necrosis with acidosis, oliguria, and proteinuria may accompany the initial overwhelming intoxication. Indeed, here in this hospital about two years ago we saw a young man who attempted to kill himself by taking a large dose of an arsenical compound. Very deep jaundice and almost complete renal shutdown developed, and then, during recovery from these conditions, severe neuropathy. Bone marrow depression has been a frequent feature in the cases we have seen here in the last few years. Leukopenia and normochromic anemia are invariably present and are thought to reflect bone marrow depression. I am unable to explain some of the features in our case today. I am unaware of porphyrinuria's having been reported with arsenic intoxication. One would wonder whether or not there was also a component of lead intoxication, in which coproporphyrinuria is an outstanding feature.

Let us now consider the toxicology and the availability of various arsenic compounds[3,4] before we go on to the neurological aspects of arsenical poisoning. Lead, calcium, and magnesium arsenate are the most common arsenicals and they are used primarily as pesticides in sprays of various kinds. Arsine gas, which is produced by reduction of these compounds, is usually an industrial hazard. Another compound that is fairly widely available, especially in the southeastern part of the United States, is copper acetoarsenite. This interesting compound, usually called Paris green, has been widely used as an insecticide on tobacco in North Carolina and Kentucky. I can remember very well having heard as a youth the complaints of tobacco growers about having to dust the tobacco at a certain stage to control worms. Every one hated to use Paris green because they could expect to have gastroenteritis during the night following a day of dusting with it. Why more people did not die or get severe peripheral neuropathy is not known. Paris green is a brilliant green color, and some of its congeners, such as emerald green and Schweinfurt green, were used as dyes in paint and wallpaper until a stop was put to this usage. There was an old wives' tale that it was dangerous to have green wallpaper because it could poison you; indeed the dye did flake and measurable concentrations of arsenic could be measured in the air of such rooms. Fortunately, these compounds are no longer used in dyes. Fowler's solution, as I have already mentioned, is apparently still occasionally used for psoriasis. Cacodylate buffer used in laboratories has a high arsenic content and represents a hazard in the laboratory.

Clinical Neuropathy

Let us now move on to the clinical neuropathy.[5-8] By and large the neuropathy is a late occurrence in the course of acute arsenic intoxication. It usually appears between the seventh and the fourteenth day after a single ingestion. It begins with tingling in the toes and fingers. If it is going to become severe, it will progress over the course of a week or two, plateau, and then take weeks and sometimes months to abate. The degree of recovery depends upon the severity of the neuropathy. Our patient has relatively mild neuropathy from the motor standpoint. He has mild distal weakness in his hands and feet, but is more disturbed by dysesthesia. Almost all patients have such severe hyperpathia in the affected parts that they are unable to tolerate light stroking of the skin or the pressure of bed clothes. This unfortunately may persist for many weeks or months after the intoxication, even when the motor paralysis has completely disappeared. What the factors are that determine whether or not someone will have persisting dysesthesias for many weeks or months is not known. Perhaps at this point I should tell you about another patient whom we saw at the Veterans Administration Hospital two or three years ago in whom another aspect of arsenical neuropathy was represented. The patient was a 50-year-old man who had married some four years previously. About a year after the marriage he began having attacks of gastrointestinal distress that would come and go every month or so. He was admitted two or three times to the Veterans Administration Hospital, but no cause was found for these episodes. He continued to be plagued by recurrent cramps, nausea, vomiting and diarrhea. Then over a period of several months he noticed increasing pigmentation of the the skin and a fluctuating but mild distal symsymmetrical polyneuropathy. We were asked to see him in consultation. We thought that he might have one of those rare neuropathic conditions seen with hemochromatosis, because of the increasing pigmentation and because of the presence of some liver disease. Accordingly, we asked the

house staff to get a serum iron determination immediately and, only as an afterthought, to send off specimens of hair and nail for arsenic analysis. The analysis revealed a 100-fold increase in the arsenic level in the nails and massive quantities in the hair. We asked the patient where he could conceivably have come into contact with arsenic. When he could think of no such exposure, we asked rather directly whether anyone might wish to harm him. He denied this possibility. We then asked if we could speak with his wife. When we did, we found it difficult to meet her eye, as she continually looked away. We told her we were afraid someone was intent on harming her husband, and asked whether she knew who it might be. Later we notified the local police authorities, and since then our patient has been in exemplary health. This is the usual situation. I have seen six patients who had an arsenical neuropathy in the past few years, and in at least four there was homicidal and in one suicidal intent. I have already referred to the latter case.

The patient who was presented today must have suffered an industrial exposure related somehow to the cleaning of the electroplating tank. I must say that I am not a toxicologist and do not know exactly what sequence of events must have taken place in the tank.

With respect to the treatment of arsenic intoxication, recent evidence indicates that there is a very real place for the use of BAL. Most of the literature before 1966 was quite equivocal about the use of this agent. For example, Heyman and his associates[5] concluded that it did not work. However, their patients were seen usually four to six weeks after the acute ingestion. By contrast, Jenkins[6] has shown very nicely that if patients are treated with BAL within the first 18 hours after ingestion, neuropathy can be forestalled. BAL is given by deep intramuscular injection several times in the first 24 hours and then once or twice daily for ten days thereafter. Thus, the early use of BAL is certainly indicated, but once neuropathic symptoms have appeared, there seems little point in subjecting a patient to the discomfort of such treatment.

DR. SMITH: *Thank you, Dr. Asbury.*

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